REMARKS

Upon entry of the foregoing amendment, Claims 59-88 will be pending in the application. Claim 74 is currently amended. Claim 88 has been withdrawn. No new matter has been introduced by way of amendment. Allowance of all pending claims is respectfully requested.

Claim Objection

Claim 74 is objected to because of the following informalities: a word is missing between the word "mutation' and the word "a partial". Claim 74 has been amended to add the word "or", as set forth above.

Rejections under 35 U.S.C. §102

Claims 59-62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Chang et al (WO 99/25860; entire document). Chang et al. is cited as generally describing adenovirus vectors that comprise a gene essential for replication under the control of a tissue specific promoter and further comprise a transgene, wherein the gene essential for replication and transgene are linked by an IRES.

Page 3 of the Office Action states that page 16 of Chang et al. teaches that the native transcriptional regulatory sequences may be rendered dysfunctional or may be disabled by partial removal (deletion) or other mutation. Page 3 of the Office Action further states that it is inherent in the design of the construct that the second promoter be deleted of its endogenous promoter as the use of an IRES is for expression of two genes using a single regulatory sequence.

Applicants respectfully disagree.

For anticipation under 35 U.S.C. § 102, the reference "must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." (MPEP §706.02). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Independent Claim 59, is directed to a replication-competent adenoviral vector for selective cytotoxicity of a target cell, comprising first and second genes co-transcribed as a single mRNA wherein the first and second genes are under transcriptional control of a heterologous, target cell-specific transcriptional regulatory element (TRE). The first gene is an adenoviral gene and the second gene has a disabled endogenous promoter and is under translational control of an internal ribosome entry site (IRES), wherein the endogenous promoter of the second gene is disabled by a mutation or a partial deletion.

Applicants respectfully submit that Chang does not anticipate Claims 59-62, 65, 67-70, 72, 74-78, 80, 81 or 84-87, however, in the interest of expediting prosecution of the above-identified application, Applicants provide herewith a declaration of prior invention under 37 CFR 1.131 by De-Chao Yu. The declaration is submitted as evidence that the subject matter claimed in the above-identified application was reduced to practice by the present inventors prior to the publication of Chang et al (WO 99/25860) on May 27, 1999.

It follows that Chang et al. should be removed as a prior art reference under 35 U.S.C. §102(a).

Rejections under 35 U.S.C. §103

Claims 59-62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chang et al (WO 99/25860; entire document).

Chang et al. is described above. On page 4, the Office Action states that Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression from the bicistron is controlled by a tissue specific regulatory element. The second gene has a mutation or partial deletion of its endogenous promoter and is under translational control of an IRES.

On page 4, the Office Action further states that Chang et al. do not teach that the second gene has a deletion in its promoter. Nanbru et al. is cited as teaching construction of a bicistronic vector for expression of a first and second coding sequence separated by a c-myc leader sequence (which comprises the native promoters as well as leader sequences). The c-myc promoters are partially deleted in the bicistronic vector. On page 5, the Office Action states that

it would have been obvious at the time the invention was made to substitute the tissue specific promoter of Chang et al., with the hK2 promoter and enhancer of Yu et al or the uroplakin II promoter of Lin et al. or the E2F promoter of Rovelink et al. because Chang et al teach that it is within ordinary skill in the art to generate a selectively replicating adenovirus by introducing a tissue specific promoter into the adenovirus and because Yu et al. and Lin et al. and Rovelink et al. teach that it is within ordinary skill to use hK2, uroplakin II or the E2F promoters for tissue specific expression. The Office Action further states that one would have been motivated to do so in order to generate potential therapeutics in which adenoviruses selectively replicate in neoplastic tissue.

Applicants respectfully disagree, and submit that Chang does not render obvious Claims 59-62, 65, 67-70, 72, 74-78, 80, 81 or 84-87, however, in the interest of expediting prosecution of the above-identified application, Applicants provide herewith a declaration of prior invention under 37 CFR 1.131 by De-Chao Yu. The declaration is submitted as evidence that the subject matter claimed in the above-identified application was reduced to practice by the present inventors prior to the publication of Chang et al (WO 99/25860) on May 27, 1999.

As stated in MPEP §2142, the examiner bears the initial burden of factually supporting a prima facie conclusion of obviousness. The examiner must show that the claimed invention was obvious to a person of ordinary skill in the art at the time the application was filed. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

For the reasons set forth above, Chang et al. should be removed as a prior art reference under 35 U.S.C. §103(a). The secondary references, Yu et al., Lin et al. and Rovelink et al. are cited as teaching promoters that could allegedly be substituted into the adenovirus vectors of Chang et al. Hence the remaining prior art references (Yu et al., Lin et al. and Rovelink et al.), taken alone or in combination do not teach or suggest all the claim limitations.

It follows that the rejection under 35 U.S.C. §103(a) should be withdrawn.

Claim 63, 64, 66 and 73 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chang et al (WO99/25860; see entire document) in view of Yu et al (Cancer Research, 1999; see entire document) or Lin et al (PNAS, 1995; see entire document) or Roelvink et al (US 2001/0047081; entire document).

Chang et al. is described above. On page 6, the Office Action states that Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression from the bicistron is controlled by a tissue specific regulatory element.

On page 6, the Office Action further states that Chang et al. do not teach that the second gene has a deletion in its promoter. Nanbru et al. is cited as teaching construction of a bicistronic vector for expression of a first and second coding sequence separated by a c-myc leader sequence (which comprises the native promoters as well as leader sequences). The c-myc promoters are partially deleted in the bicistronic vector. On pages 6 and 7, the Office Action states that it would have been obvious at the time the invention was made to substitute the tissue specific promoter of Chang et al., with the hK2 promoter and enhancer of Yu et al or the uroplakin II promoter of Lin et al. or the E2F promoter of Roelvink et al. because Chang et al teach that it is within ordinary skill in the art to generate a selectively replicating adenovirus by introducing a tissue specific promoter into the adenovirus and because Yu et al. and Lin et al. and Roelvink et al. teach that it is within ordinary skill to use hK2, uroplakin II or the E2F promoters for tissue specific expression. The Office Action further states that one would have been motivated to do so in order to generate potential therapeutics in which adenoviruses selectively replicate in neoplastic tissue.

Applicants respectfully disagree, and submit that Chang et al., taken together with Yu et al. and Lin et al. do not render obvious Claim 63, 64, 66 or 73, however, in the interest of expediting prosecution of the above-identified application, Applicants provide herewith a declaration of prior invention under 37 CFR 1.131 by De-Chao Yu. The declaration is submitted as evidence that the subject matter claimed in the above-identified application was reduced to

practice by the present inventors prior to the publication of Chang et al (WO 99/25860) on May 27, 1999.

It follows that the primary reference, Chang et al. should be removed as a prior art reference under 35 U.S.C. §103(a). The secondary references, Yu et al., Lin et al. and Rovelink et al. are cited as teaching promoters that could allegedly be substituted into the adenovirus vectors of Chang et al. As set forth above, Yu et al., Lin et al. and Rovelink et al., taken alone or in combination do not teach or suggest all the claim limitations. Hence, the obviousness under 35 U.S.C. §103(a) does not lie and the rejection should be withdrawn.

Claim 71 and 79 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Perez and White (Journal of Cell Biology, 1998; entire document).

Chang et al. is described above. On page 7, the Office Action states that Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression from the bicistron is controlled by a tissue specific regulatory element.

On page 7, the Office Action further states that Chang et al. do not teach use of Fas as the cytotoxic gene in which E1B 19K is deleted. Perez and White are cited as teaching Fas mediated apoptosis leads to cell killing triggered by Fas ligand and that E1B 19K blocks Fas-mediated apoptosis. On pages 7 and 8, the Office Action states that it would have been obvious at the time the invention was made to substitute the cytotoxic gene of Chang et al with a Fas gene in which E1B 19K is deleted because Chang et al teach that it is within ordinary skill in the art to express a cytotoxic gene from an adenovirus for cell killing and because Perez and White teach that Fas mediated cell killing is blocked by E1B 19K. The Office Action further states that one would have been motivated to do so in order to enhance cell killing.

Applicants respectfully disagree, and submit that Chang et al., taken together with Perez and White do not render obvious Claim 71 or 79, however, in the interest of expediting prosecution of the above-identified application, Applicants provide herewith a declaration of prior invention under 37 CFR 1.131 by De-Chao Yu. The declaration is submitted as evidence

that the subject matter claimed in the above-identified application was reduced to practice by the present inventors prior to the publication of Chang et al (WO 99/25860) on May 27, 1999.

It follows that the primary reference, Chang et al. should be removed as a prior art reference under 35 U.S.C. §103(a). The secondary references, Perez et al. and White et al. are cited as teaching a Fas gene in which E1B 19K is deleted that could allegedly be substituted into the adenovirus vectors of Chang et al. Perez et al. and White et al. taken alone or in combination do not teach or suggest all the claim limitations. Hence, the obviousness under 35 U.S.C. §103(a) does not lie and the rejection should be withdrawn.

Claim 82 and 83 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chang et al (WO 99/25860; entire document) in view of Stein et al (Molecular and Cellular Biology 1998; entire document) or Borman et al (NAR, 1995; entire document).

Chang et al. is described above. On page 8, the Office Action states that Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression from the bicistron is controlled by a tissue specific regulatory element.

On page 8, the Office Action further states that Chang et al. do not teach use of specific IRES sequences such as from EMCV or VEGF. Stein et al. and Borman et al. are cited as teaching EMCV and VEGF IRESs. On page 9, the Office Action states that it would have been obvious at the time the invention was made to substitute the IRES of Chang et al with an EMCV or VEGF IRES because Chang et al teach that it is within ordinary skill in the art to use an IRES for bicistronic expression. The Office Action further states that one would have been motivated to do so in order to achieve cap-independent translation when overall protein synthesis is compromised or for highly efficient expression.

Applicants respectfully disagree, and submit that Chang et al., taken together with Stein et al. and Borman et al. do not render obvious Claim 82 or 83, however, in the interest of expediting prosecution of the above-identified application, Applicants provide herewith a declaration of prior invention under 37 CFR 1.131 by De-Chao Yu. The declaration is submitted as evidence that the subject matter claimed in the above-identified application was reduced to

practice by the present inventors prior to the publication of Chang et al (WO 99/25860) on May 27, 1999.

It follows that the primary reference, Chang et al. should be removed as a prior art reference under 35 U.S.C. §103(a). The secondary references, Stein et al. and Borman et al. are cited as teaching EMCV and VEGF IRESs that could allegedly be substituted into the adenovirus vectors of Chang et al. Stein et al. and Borman et al. taken alone or in combination do not teach or suggest all the claim limitations. Hence, the obviousness under 35 U.S.C. §103(a) does not lie and the rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for examination on the merits. Early notification of such action is earnestly solicited. If any issues remain which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact Applicants counsel, Linda R. Judge at (415) 836-2586.

Respectfully submitted,

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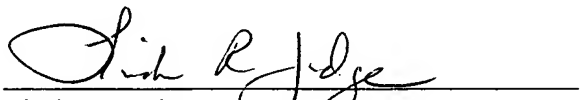

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